**Remarks/Arguments:**

Claims 91 and 97, currently amended, claims 92-96, previously presented, and claim 133, presented hereby, are pending.

Claims 1-90 and 98-132 are canceled.

Claim 91 is amended, hereby in order to delete redundant text appearing at the end of the claim. Claim 97 is amended, hereby, by deleting "essentially" from the limitation "which substitution essentially ensures preservation of the β-sheet structures of the B and G strands." By deleting "essentially," the limitation, now, requires that the structural integrity of the B-strand β-sheet and the G-strand β-sheet must be preserved.

Applicants wish to thank Primary Examiner David Romeo for the timely indication of allowable subject matter in the present office action (page 6), i.e., overcoming the outstanding claim objection would render claims 91-96 allowable.

Claims 91-96 were objected to because text appearing at the end of claim 91 was inadvertently repeated in the claim. The objection is overcome by the instant amendment, which deletes the redundant language from claim 91. Accordingly, the objection being overcome, claims 91-96, as presently amended, are allowable, in accordance with the instant office action.

Claim 97 stands rejected under 35 USC 103(a) as being allegedly unpatentable based on the teachings of WO 95/05849 (Mouritsen) combined with *Nature, 312*, 724-729, 1984 (Pennica), *Nature, 313*, 803-806, 1985 (Shirai), or *Science 228*, 149-154, 1985 (Wang), and further in view of Crystal structure of TNF, *Tumor Necrosis Factors, Structure, Function, and Mechanism of Action*,

Ch. 5, 93-127, New York, 1992 (Jones), and *Eur. J. Immunol, 19*, 2237-2242, 1989 (Panina-Bordignon) and US5656272 (Le), and further in view of WO93/05810 (Hellman), WO92/19746 (Cox), and "Immunoglobulin signal transduction guides the specificity of B cell-T cell interactions and is blocked in tolerant self-reactive B cells," *J Exp Med., 179*, 1994, 425-38 (Cooke). Reconsideration is requested.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art," *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970), "and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982). A "ground of rejection is simply inadequate on its face . . . [when] the cited references do not support each limitation of [the] claim." *In re Thrift*, 63 USPQ2d 2002, 2008 (Fed. Cir. 2002).

When the claimed invention requires modification of the prior art, there is no obviousness under §103 when "[t]he prior art does not suggest . . . [the] modification . . . or provide any reason or motivation to make the modification." *In re Laskowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989).

> In order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*,[1] preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention [*citations, omitted*].

*Ex parte Levengood*, 28 USPQ2d 1300, 1300-01 (BPA&I 1993)(*emphasis in original*). The fact that all elements of a claimed invention are known does not, by itself, make the combination obvious. *Ex parte Clapp*, 227 USPQ 972 (BPA&I 1985). To support a rejection for obviousness based on the combination of separate prior art teachings, the PTO "must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *In re Rouffet*, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998).

To reject claims for obviousness under §103 based on modifying the teachings of a reference, existence in the prior art of a reason (motivation) to effect the modification is not, by itself, sufficient to sustain the initial burden on the PTO; the "record" must show

> . . . that it would also have been obvious *how* this [modification] could be achieved . . . . Obviousness . . . must not be judged by hindsight, and a "little modification" can be a most unobvious one.

*In re Irani*, 166 USPQ 24, 27 (CCPA 1970) (*emphasis in original*). Prior art relied on in a rejection under §103 must be *enabling*, i.e., "if the prior art of record fails to disclose or render obvious a method of making the claimed [invention] . . . it may not be legally concluded that the compound was in the possession of the public. *In re Hoeksema*, 158 USPQ 596, 601 (CCPA 1968).

The §103(a) rejection relies on Mouritsen, Pennica, Wang, Jones, Panina-Bordignon, and Le "as discussed in the last [Final] Office Action" (present Office Action, page 3). As set forth in the Final Office Action (page 4) Mouritsen does not disclose a "TNF2-1 variant," but the reference does disclose an MR105 variant. While this is correct, the presently disclosed (but not claimed) variant TNF2-1—a variant of human TNF—is the human-derived equivalent of MR105.

It is also alleged in the Final Action (page 4) that the present application acknowledges that TNF variants disclosed in Mouritsen provide for induction of neutralizing antibodies. This in not correct; the subject application does *not* acknowledge that TNF variants disclosed in Mouritsen provide for induction of neutralizing antibodies.

The subject application discloses that variants MR103 and MR106 provide for the induction of neutralizing antibodies. On the other hand, with respect to MR105, the subject application merely teaches that MR105 provides for a higher antibody titer than a murine TNF conjugated to an *E. coli* protein.

Moreover, it is important to remember that the results discussed in the paragraph bridging pages 35 and 36 of the subject application cannot be relied on as if they were in the prior art. In point of fact, the results were published only after the present application's priority date. Any disclosure in the subject application that is not found in the prior art cannot be used as if it were found in the prior art, i.e., the disclosure cannot be used in applying the teachings of Mouritsen against the instant claims. *Ex parte Obukowicz*, 27 USPQ 1063, 1065 (BPA&I 1992). Applicant's own teachings cannot be read into the prior art. *In re Deminsky*, 230 USPQ 313 (Fed. Cir. 1986).

The point (as previously made) is that MR105 is the murine equivalent to the presently disclosed, human-derived TNF2-1. Since MR105 is the only variant disclosed in Mouritsen that is demonstrated to be biologically inactive, i.e., non-toxic (Mouritsen, page 12, lines 15-16), the skilled artisan would have, only, expected that optimum variants of human TNF must resemble the MR105 variant of Mouritsen if one wishes to prepare non-toxic variants as presently claimed. There is

certainly nothing in Mouritsen that would have led the skilled artisan to prepare variants of human TNF that preserve the β-sheet structure of the B and G strands, as recited in the present claims. Since nothing in the other cited references provides the requisite motivation lacking in Mouritsen, the rejection under §103(a) cannot be maintained. *Laskowski, supra. Levengood, supra. Rouffet, supra.*

With respect to the stated reliance on Le, if one were to accept the argument that Le provides the requisite motivation for the skilled person to induce neutralizing antibodies against TNF, then the skilled person would not have been be able to deduce from Mouritsen anything that points in direction of the necessity of preserving the β-sheet structure of the B and G strands of human TNF.

With respect to the stated reliance on Jones (Final Action, page 5), reading Jones would have led one skilled in the art to expect that TNF variants capable of inducing neutralizing antibodies could be produced, which applicants do not dispute. However, the PTO has not addressed (shown) how the skilled person would have expected immunogenic TNF variants could be *both* non-toxic (as taught in Mouritsen) *and* capable of inducing neutralizing antibodies, as taught in Jones. The present claim limitation to preservation of B-strand β-sheet structure and G-strand β-sheet structure cannot be derived from Jones, Mouritsen or any other cited references, taken alone or in combination with one another. Accordingly, one skilled in the art would have had to engage in undue experimentation to arrive at the presently claimed subject matter, i.e., the cited references would not have enabled one skilled in the art to arrive at the presently claimed invention and, so, the rejection under §103(a) cannot be maintained. *Irani, supra. Hoeksema, supra.*

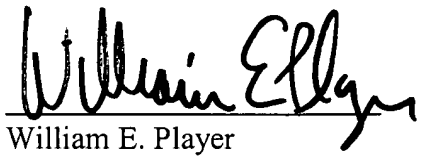
Applicants submit that, in order to arrive at the presently claimed invention, given the teachings of the cited references, the skilled artisan, first, would have had to realize that the MR105 variant of Mouritsen is an unsuitable starting point for designing non-toxic variants of human TNF and, secondly, would have had to engage in undue experimentation in order to identify those variants that actually fulfil the criteria of non-toxicity *and* capability of inducing neutralizing antibodies. In other words, the skilled artisan would have had to *invent* the subject matter of claim 97, which demonstrates *non*-obviousness—rather than obviousness—under §103(a).

Notwithstanding the foregoing, the instant amendment to claim 97 overcomes the rejection of the claim under §103(a). In rejecting claim 97 the statement of rejection (Final Action, page 5) maintains that the claim language allows "some substitution of the B and G strands." As explained above, the limitation "which substitution essentially ensures preservation of the β-sheet structures of the B and G strands" is amended, hereby, to read "which substitution ensures preservation of the β-sheet structures of the B and G strands," which requires that the β-sheet structures of the B and G strands must be preserved in order to meet the limitation on present claim 97 (as true, also, with respect to newly added claim 133). In other words, the language of (amended) claim 97 does *not* allow "some substitution of the B and G strands" and, so, a limitation on present claim 97 not being supported by the cited references, the rejection under §103(a) cannot be maintained against present claim 97. *Royka, supra. Thrift, supra.*

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By 

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